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Models for estimating the biological age of five organs using clinical biomarkers that are commonly measured in clinical practice settings

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ABSTRACT

Objectives: To date, no worldwide studies have been conducted to estimate the biological age of five organs using clinical biomarkers that are associated with the aging status. Therefore, we conducted this study to develop the models for estimating the biological age of five organs (heart, lung, liver, pancreas, and kidney) using clinical biomarkers which are commonly measured in clinical practice.
Design: A cross sectional study.
Methods: Subjects were recruited from the routine health check-up centers in Korea from 2004 through 2010. Data obtained from 121,189 subjects (66,168 men and 55,021 women) were used for clinical evaluation and statistical analysis. We examined the relations between clinical biomarkers associated with five organs and the chronological age and proposed a model for estimating the biological age of five organs.
Results: In the models for predicting the biological ages of the heart, lung, liver, pancreas and kidney in men, 12, 2, 8, 3, and 5 parameters were respectively included (R^2 = 0.652, 0.427, 0.107, 0.245, and 0.651). In contrast to men, 10, 2, 8, 3, and 5 parameters in women were respectively included (R^2 = 0.780, 0.435, 0.140, 0.384, and 0.501).
Conclusion: We first proposed the models for predicting the biological age of five organs in the current study. We developed those using clinical parameters that can be easily obtained in clinical practice settings. Our biological age prediction models may be used as supplementary tools to assess the aging status of five organs in clinical practice settings.

1. Introduction

Aging in humans refers to a multidimensional process of physical, psychological, and social changes that occur since birth. Aging changes may be good such as acquisition of wisdom or adverse such as a time-related decline in physiological functions and changes in morphology [1].

Aging is usually assessed by the chronological age, which is defines as time elapsed since birth. However, chronological age fails to provide accurate indicator of the aging process [2]. Biological age estimates the functional status of an individual in reference to his or her chronological peers on the basis of how well he or she functions in comparison with others of the same chronological age [3]. Different individual rates of the aging process lead to differences between chronological age and biological age, thus individual

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values of biological age can vary widely at any given chronological age, and ultimately are expected to correspond to the inter-individual variations in longevity and timing and/or magnitude of sequelae of the aging process [4,5]. It has been proposed that biological age may serve as an indicator of an individual's general health status, remaining healthy life span, and active life expectancy [6].

Any biological parameter that is correlated with chronological age of an organism can be referred to as a biomarker of aging in its simplest application; however, this application is purely descriptive. Regarding its more complex application, a biomarker of aging is meant to provide more useful information about the aging process than can be provided by the chronological age of the organism. The term refers to a biological parameter intended as a quantitative measure of the rate of aging more accurate than chronological age [7]. The concept of biological age may be best represented by the construction of an index derived from several biological parameters of an organism, which are closely related to the maintenance of life and correlated to some degree with chronological age [8].

There is still no direct way to measure biological age. Therefore, many gerontologists have tried to develop a test battery as an indirect method that measures a number of functions known to change significantly with age. The test battery should provide a more accurate estimate of biological age than is possible by simple observation and merely guessing at someone's chronological age. They combined a series of diverse tests into a single value that correlate with chronological age by statistical analysis, such as multiple regression analysis. At the present time, the best means to measure biological age and aging rates is to develop a test battery with a number of aging biomarkers known to change significantly with chronological age.

Because tissues and organs age at different rates, there is a need to obtain biomarkers from multiple systems and to combine them in the most efficient way to reflect overall aging of an organism. Aging biomarkers can be classified based on such body organs as cardiovascular, pulmonary, renal, muscular, skin, immune systems, and so on [9]. Therefore, if the biological age is measured using an extensive scale of biomarkers, it would provide us with measures to determine the status and rate of aging more than the chronological age in individuals. From a similar perspective, if the biological age of each body organ is measured accurately, it would be mandatory to test a variety of biomarkers reflecting its functional status.

The concept of biological age has been widely investigated since the 1970s. Most studies have been made simply on an academic-research level with limited biomarkers [3,6,10–15]. In recent years, a multi-center joint study has developed a model for predicting biological age that may be applied to clinical practice settings [16]. To date, no worldwide studies have been conducted to estimate the biological age of five organs using clinical biomarkers that are associated with the aging status. Given the above background, we conducted this study to develop the models for estimating the biological age of five organs (heart, lung, liver, pancreas, kidney) using clinical biomarkers which are commonly measured in clinical practice.

2. Materials and methods

2.1. Subjects

The current study was conducted on 121,189 subjects aged 20 years or older, comprising 66,168 men and 55,021 women, who received routine health check-ups from 2004 through 2010 at the university medical centers and community hospitals in Korea. Written informed consent was obtained from all participants.

To evaluate the actual changes of each subject's organ functions according to the normal aging process, we excluded through health examinations people who were proven to have serious diseases such as cancer, malignant hypertension, uncontrolled diabetes and cardiac, pulmonary, hepatic, pancreatic, and renal insufficiency. We also excluded anyone who was taking medications for hypertension, diabetes mellitus, dyslipidemia, hepatic disease, pancreatic disease, or renal disease.

2.2. Clinical biomarkers

A routine health check-up included anthropometric measurements, cardiovascular and respiratory functions, and laboratory tests (blood and urine). Height, weight, lean body mass, and body fat mass were measured using a multi-frequency segmental bioelectrical impedance, the InBody (Biospace, Korea). Body index was calculated by the weight in kilograms divided by the square of the height in meters. Waist and hip circumferences are measured with a tapeline. As for the waist circumference, the thinnest area between the inferior part of the lowest rib and the iliac crest was measured in an upright position. In addition, as for the hip circumference, the location of greater trochanter or the widest circumference was measured. Blood pressure was measured manually using a sphygmomanometer after resting 5 min in a sitting position. Both forced vital capacity and forced expiratory volume in 1 s were measured by an electronic spirometer two times in standing position, and better record was obtained. Blood samples were drawn from the antecubital space in the morning after an overnight fasting long than 10 h.

In this study, the candidate biomarkers of aging should reflect specific human functions which change uniformly not due to disease processes, but due to the simple aging process in the normally aging person. It is sometimes very difficult to define specific values, which distinguish normal aging process from abnormal one. So the inclusion criteria of normality were determined by physicians who participated in this study with somewhat broader ranges when compared with general clinical normality criteria. Finally, we set inclusion criteria considering the means and standard deviations of biomarkers that were collected and the normal range which was established by the American Medical Association (AMA) (Table 1). The inclusion criteria of normality were prepared usually using mean $\pm$ 3 to 4 SD with some exceptions depending on the disease criteria of AMA and distribution of study variables.

Of the clinical indicators that were collected, we selected only those which were associated with aging of each body organ reported in previous studies, or showed statistically significant correlations with age. We classified the clinical biomarkers into cardiac, pulmonary, hepatic, pancreatic, and renal parameters. A profile of cardiac parameters included body mass index (BMI), lean body mass % (LBM%), body fat % (BF%), waist circumference (WC), waist-hip ratio (WHR), systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), total cholesterol (TC), high-density lipoproteins (HDL), triglycerides (TG), low-density lipoproteins (LDL) and homocysteine. A profile of pulmonary parameters included forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1). A profile of hepatic parameters included total protein, albumin, albumin–globulin ratio (AGR), alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (G-GTP), total bilirubin and direct bilirubin. A profile of pancreatic parameters included fasting blood sugar (FBS), hemoglobin A1c (HbA1c) and amylase. Finally, a profile of renal parameters included creatinine, creatinine clearance (CrCl), blood urea nitrogen (BUN), urine specific gravity (USG) and urine PH (UPH).